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Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet	1	of	3	Attorney Docket Number	28646/42267
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Complete if Known

Application Number	10/590,789
Filing Date	August 25, 2006
First Named Inventor	Roger Melton
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	28646/42267

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
		US-20040014187-A1	01-22-2004	Springer et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ³
		Country Code ⁴ -Number ⁴ -Kind Code ⁵ (if known)				
		EP 0 12 352	10-10-1984	Atkinson et al.		

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Abelson et al., "High-Dose Methotrexate-Carboxypeptidase G ₁ -A Selective Approach to the Therapy of Central Nervous System Tumors", <i>Developments in Biochemistry</i> , 4:629-634 (1979)	
		Adamson et al., "Rescue of Experimental Intrathecal Methotrexate Overdose with Carboxypeptidase-G ₂ ", <i>J. Clin. Oncol.</i> , 9:670-674 (1991).	
		Adamson et al., "Methotrexate Pharmacokinetics Following Administration of Recombinant Carboxypeptidase-G ₂ in Rhesus Monkeys", <i>Journal of Clinical Oncology</i> , 10:1359-1364 (1992)	
		Bleyer, "The Clinical Pharmacology of Methotrexate. New Applications for an Old Drug," <i>Cancer</i> , 41:36-51 (1978).	
		Bloom et al., "The anticancer AG2037 utilizes hypoxanthine salvage as an important rescue mechanism", <i>Proc Amer Assoc Cancer Res Annu Meet</i>, 48:50	
		Castro, "Thymidine rescue: an antidote for pemetrexed-related toxicity in the setting of acute renal failure", <i>J. Clin. Oncol.</i> , 21:4066 (2003)	
		Chabner et al., "Enzymatic Cleavage of Methotrexate Provides a Method for Prevention of Drug Toxicity," <i>Nature</i> , 239:395-397 (1972)	
		Chambers et al., "Plasmid pMTL153: a high copy number version of pAT153 and its use to obtain high expression of the <i>Pseudomonas carboxypeptidase G₂</i> gene", <i>Appl. Microbiol. Biotechnol.</i> , 29:572-578 (1998)	
		Clarke et al., "Clinical and Preclinical Pharmacokinetics of Raltitrexed," <i>Clin. Pharmacokinet</i> , 39(6):429-443 (2000)	
		Condit et al., "Renal Toxicity of Methotrexate," <i>Cancer</i> , 23:126-131 (1969)	
		DeAngelis et al., "Carboxypeptidase G ₂ Rescue After High-Dose Methotrexate", <i>Journal of Clinical Oncology</i> , 14:2145-2149 (1996)	
		Dowell et al., "New Mustard Prodrugs for Antibody-Directed Enzyme Prodrug Therapy: Alternatives to the Amide Link," <i>J. Med. Chem.</i> , 39:1100-1105 (1996)	
		Dreicer et al., "A Phase II Trial of Edatrexate in Patients with Advanced Renal Cell Carcinoma", <i>Am. J. Clin. Oncol.</i> , 20(3):251-253 (1997)	
Examiner Signature		Date Considered	

No date

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JDA/

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				Art Unit	Not Yet Assigned
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Sheet	2	of	3	Attorney Docket Number	28646/42267

	Farrugia et al., "Leucovorin Rescue from Raltitrexed (Tomudex)-induced Antiproliferative Effects: <i>In Vitro</i> Cell Line and <i>In Vivo</i> Mouse Studies", <i>Clinical Cancer Research</i> , 6:3646-3656 (2000)	
	FDA grants orphan drug designation for voraxaze, Protherics PLC (2003)	
	Franchi et al., "Favorable Toxicity Profile of Raltitrexed in Elderly Patients Treated for Colorectal Cancer: A Case Series," <i>Gerontology</i> , 49(5):324-327 (2003)	
	Goldman, "Membrane Transport of Methotrexate (NSC-740) and Other Folate Compounds: Relevance to Rescue Protocols," <i>Cancer Chemo Rep.</i> , 6:63-72 (1975)	
	Jackman et al., "ICI D1694, a Quinazoline Antifolate Thymidylate Synthase Inhibitor That is a Potent Inhibitor of L1210 Tumor Cell Growth <i>In Vitro</i> and <i>In Vivo</i> : A New Agent for Clinical Study", <i>Cancer Research</i> , 51:5579-5586 (1991)	
	Johansen et al., "Final results of a phase I and pharmacokinetic study of γ -methylene-10-deazaaminopterin (MDAM) administered intravenously daily for five consecutive days in patients with solid tumors", <i>Cancer Chemother. Pharmacol.</i> , 53:370-376 (2004)	
	Jolivet et al., "The Pharmacology and Clinical Use of Methotrexate," <i>N. Engl. J. Med.</i> , 309:1094-1104 (1983)	
	Kalghatgi et al., "Folate-Degrading Enzymes: A Review with Special Emphasis on Carboxypeptidase G," <i>In: Enzymes as Drugs</i> , J Holcenberg and J Roberts, eds, Wiley, New York, pp.77-102 (1981).	
	Kintzel, "Anticancer Drug-Induced Kidney Disorders," <i>Drug Safety</i> , 24:19-38 (2001)	
	Kisliuk, "Deaza Analogs of Folic Acid as Antitumor Agents," <i>Current Pharmaceutical Design</i> , 9(31):2615-2625 (2003).	
	Krackhardt et al., "Carboxypeptidase G ₂ Rescue in a 79 Year-Old Patient With Cranial Lymphoma After High-Dose Methotrexate Induced Acute Renal Failure", <i>Leuk. Lymph.</i> , 35:631-635 (1999)	
	Krause et al., "Carboxypeptidase-G ₂ Rescue in Cancer Patients with Delayed Methotrexate Elimination after High-dose Methotrexate Therapy", <i>Leukemia and Lymphoma</i> , 43(11):2139-2143 (2002)	
	Krug et al., "Phase I and Pharmacokinetic Study of 10-Propargyl-10-deazaaminopterin, a New Antifolate ¹ ", <i>Clinical Cancer Research</i> , 6:3493-3498 (2000)	
	Kuriakose et al., "Phase I Trial of Edatrexate in Advanced Breast and Other Cancers", <i>Cancer Investigation</i> , 20(4):473-479 (2002)	
	Mantadakis et al., "Delayed Methotrexate Clearance in a Patient With Sickle Cell Anemia and Osteosarcoma", <i>J. Pediat. Hematol. Oncol.</i> , 21:165-169 (1999)	
	Massacesi et al., "Raltitrexed-Induced Hepatotoxicity: Multivariate Analysis of Predictive Factors," <i>Anticancer Drugs</i> , 14(7):533-541 (2003).	
	McCullough et al., "Purification and Properties of Carboxypeptidase G ₁ ," <i>J. Biol. Chem.</i> , 246:7207-7213 (1971).	
	McGuire, "Anticancer Antifolates: Current Status and Future Directions," <i>Current Pharmaceutical Design</i> , 9(31):2593-2613 (2003)	
	Meyers et al., "Phase II trial of edatrexate in relapsed or refractory germ cell tumors: A Southwest Oncology Group Study (SWOG 9124)", <i>Investigational New Drugs</i> , 16:347-351 (1999)	
	Minton et al., "Molecular Cloning of the <i>Pseudomonas</i> Carboxypeptidase G ₂ Gene and its Expression in <i>Escherichia coli</i> and <i>Pseudomonasputida</i> ," <i>J. Bacteriol</i> , 156:1222-1227 (1983)	
	Minton et al., "The Complete Nucleotide Sequence of the <i>Pseudomonas</i> Gene Coding for Carboxypeptidase G ₂ ," <i>Gene</i> , 31(1-3):31-38 (1984)	
	Minton et al., "Identification of the Promoter of the <i>Pseudomonas</i> Gene Coding for	

Examiner Signature		Date Considered	
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	Carboxypeptidase G2," <i>J. Mol. Appl. Genet.</i> , 3(1):26-35 (1985)	
	Mohty et al., "Carboxypeptidase G2 Rescue in Delayed Methotrexate Elimination in Renal Failure," <i>Leuk. Lymphoma</i> , 37:441-443 (2000)	
	Nguyen et al., "Pharmacokinetics studies and toxicity profile of raltitrexed used by intraperitoneal route in normothermia in a pig model", <i>Med. Sci. Monit.</i> , 9(1):BR37-42 (2003)	
	O'Marcaigh et al., "Successful Treatment of Intrathecal Methotrexate Overdose by Using Ventriculolumbar Perfusion and Intrathecal Instillation of Carboxypeptidase G ₂ ", <i>Mayo Clin. Proc.</i> , 71:161-165 (1996)	
	Patterson et al., "Thymidine Phosphorylase Moderates Thymidine-dependent Rescue after Exposure to the Thymidylate Synthase Inhibitor ZD1694 (Tomudex) <i>In Vitro</i> ", <i>Cancer Research</i> , 58:2737-2740 (1998)	
	Pinedo et al., "The Reversal of Methotrexate Cytotoxicity to Mouse Bone Marrow Cells by Leucovorin and Nucleosides," <i>Cancer Res.</i> , 36:4418-4424 (1976).	
	Pisters et al., "High-Dose Edatrexate with Oral Leucovorin Rescue: A Phase I and Clinical Pharmacological Study in Adults with Advanced Cancer", <i>Clinical Cancer Research</i> , 2:1819-1824 (1996)	
	Purcell et al., "Novel Antifolate Drugs," <i>Current Oncology Reports</i> , 5(2):114-125 (2003).	
	Rowell et al., "Crystal Structure of Carboxypeptidase G ₂ , a Bacterial Enzyme with Applications in Cancer Therapy," <i>Structure</i> , 5(3):337-347 (1997).	
	Sherwood et al., "Purification and Properties of Carboxypeptidase G ₂ from <i>Pseudomonas sp.</i> Strain RS-16. Use of a Novel Triazine Dye Affinity Method," <i>Eur. J. Biochem.</i> , 148:447-453 (1985)	
	Springer et al., "Optimization of Alkylating Agent Prodrugs Derived from Phenol and Aniline Mustards: A New Clinical Candidate Prodrug (ZD2767) from Antibody-Directed Enzyme Prodrug Therapy," <i>J. Med. Chem.</i> , 38:5051-5065 (1995).	
	Summary of Product Characteristics: Voraxaze™ (Carboxypeptidase G2) Enact Pharma plc, 2003.	
	Thödtmann et al., "A phase II trial of pemetrexed in patients with metastatic renal cancer", <i>Investigational New Drugs</i> , 21:353-358 (2003)	
	Thompson et al., "Improving the Sensitivity of Progressive Multiple Sequence Alignment through Sequence Weighting, Position-Specific Gap Penalties and Weight Matrix Choice," <i>Nucleic Acids Res.</i> , 22:4673-4680 (1994).	
	"Tomudex" Patient Information Leaflet P003746, Astra Zeneca (2001)	
	Tsavaris et al., "Raltitrexed (Tomudex) Administration in Patients with Relapsed Metastatic Colorectal Cancer After Weekly Irinotecan/5-Fluorouracil/Leucovorin Chemotherapy," <i>BMC Cancer</i> , 2(1):2 (2002).	
	Von Poblozki et al., "Carboxypeptidase-G2 Rescue in a Woman with Methotrexate-Induced Renal Failure," <i>Med. Klin.</i> , 95:457-460 (2000).	
	Widemann et al., "Carboxypeptidase-G ₂ , Thymidine, and Leucovorin Rescue in Cancer Patients with Methotrexate-Induced Renal Dysfunction", <i>Journal of Clinical Oncology</i> , 15:2125-2134 (1997)	
	Widemann et al., "Rescue with Carboxypeptidase-G ₂ (CPDG ₂) and Leucovorin (LV) for Patients with High-Dose Methotrexate (HDMTX) Induced Renal Failure", <i>Proc Annu Meet Am Soc Clin Oncol.</i> , 17:A855 (1998)	
	Widemann et al., "Pharmacokinetics and Metabolism of the Methotrexate Metabolite 2,4-Diamino-N10-Methylpterioic Acid," <i>J. Pharmacol. Expel. Therapy</i> , 294:894-901 (2000).	
	Zoubek et al., "Successful Carboxypeptidase G2 Rescue in Delayed Methotrexate Elimination Due to Renal Failure", <i>Pediatric and Hematology and Oncology</i> , 12:471-477 (1995)	

Examiner Signature	/James Anderson/	Date Considered	06/28/2010
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